ABSTRACT OF THE INVENTION

A new method to analyze and predict the binding energy for enzyme-transition state inhibitor interactions is presented. Computational neural networks are employed to discovery quantum mechanical features of transition states and putative inhibitors necessary for binding. The method is able to generate its own relationship between the quantum mechanical structure of the inhibitor and the strength of binding. Feed-forward neural networks with back propagation of error can be trained to recognize the quantum mechanical electrostatic potential at the entire van der Waals surface, rather than a collapsed representation, of a group of training inhibitors and to predict the strength of interactions between the enzyme and a group of novel inhibitors. The experimental results show that the neural networks can predict with quantitative accuracy the binding strength of new inhibitors. The method is in fact able to predict the large binding free energy of the transition state, when trained with less tightly bound inhibitors. The present method is also applicable to prediction of the binding free energy of a ligand to a receptor. The application of this approach to the study of transition state inhibitors and ligands would permit evaluation of chemical libraries of potential inhibitory, agonistic, or antagonistic agents. The method is amenable to incorporation in a computer-readable medium accessible by general-purpose computers.